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(54) **Inhibition of hirsutism and alopecia in women**

Hemmung von Hirsutismus und Alopecia bei Frauen

Inhibition de l'hirsutisme et de l'alopécie chez les femmes

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(56) References cited:
US-A- 4 418 068 **US-A- 4 859 585**

- **J. ROYAL SOC. MED., vol. 83, no. 10, 1990 pages 647-648, C.B. ARCHER ET AL. 'Alopecia neoplastica responsive to tamoxifene'**
- **THE PROSTATE, vol. 23, no. 3, 1993 pages 245-262, B.L. NEUBAUER ET AL. 'Endocrine and antiprostatic effects of raloxifene (LY156758) in the male rat'**

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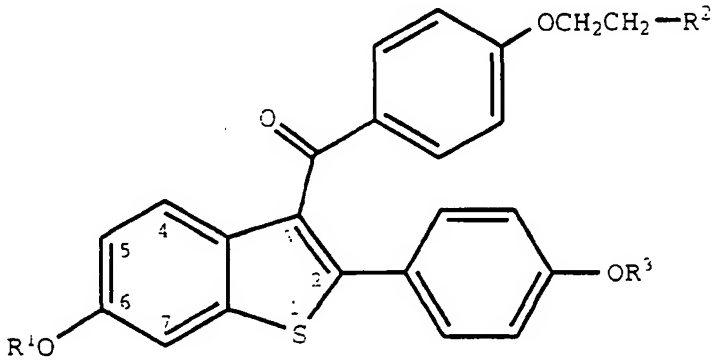
D scription

[0001] Hirsutism (hypertrichosis) is characterized by excessive growth of hair. In women, hirsutism refers specifically to excessive growth of hair in a male pattern and distribution. Clinically, hirsutism in women is seen as a growth of terminal hair on the face (particularly on the upper lip), the chin, chest, back, and lower abdomen (escutcheon). This growth of hair is often seen as unsightly and can be the cause of embarrassment and psychological distress. Hirsutism is a common occurrence at the menopause, but can occur any time after puberty. The etiology of the condition has been linked to over production of androgens by either the ovaries or adrenal glands or both.

[0002] Hirsutsim in women can be treated in a variety of ways. Cosmetic treatment of the condition, including shaving, plucking of hairs, and bleaching, while effective in improving the appearance of the patient, are only palliative and must be constantly re-applied. Glucocortacoid steroids are often effective; however, they have the potential of serious side-effects such as Cushing's Syndrome. Oral contraceptives can be effective; however, care must be taken because certain progestins used in common oral contraceptive regiments may actually contribute hirsutism because of their androgenic side-effects. Cimetidine and Spironolactone have shown some effectiveness in the treatment of hirsutism; however, each of these can have unwanted side-effects. Clearly, a more effective and better tolerated agent would be useful.

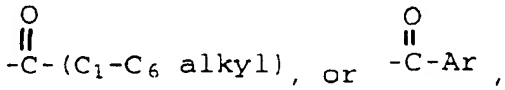
[0003] Alopecia (hair loss) can occur in women for a variety of reasons, and includes female pattern alopecia. Female pattern alopecia is characterized by chronic and progressive hair loss often beginning around thirty years of age and accelerating at menopause. The hair loss is usually confined to thecentral scalp in a diffuse pattern. This loss of hair is cosmetically damaging and often psychologically disturbing to the patient. The etiology of the condition has been linked to an elevated level of androgens and the subsequent response of androgen sensitive hair follicles. Treatment of the condition is primarily cosmetic in nature, e. g., wigs, hair styles which cover the effected area, etc. The drug, Spironolactone, has been used, but does have side-effects. Clearly, an effective treatment for this condition would be useful.

[0004] This invention provides the use of a compound of formula I



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$,



wherein Ar is optionally substituted phenyl;
R^2 is selected from pyrrolidino, hexamethyleneimino, and piperidino; and pharmaceutically acceptable salts and solvates thereof for the preparation of a medicament for inhibiting hirsutism or alopecia in women.

[0005] The current invention concerns the discovery that a select group of 2-phenyl-3-aroylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting alopecia or hirsutism in women. The methods of treatment provided by this invention are practiced by administering to a human in need a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit alopecia or hirsutism. The term inhibit is defined to include its generally accepted meaning which includes prophylactically creating a human subject to incurring

a problem described, and holding in check and/or treating an existing problem. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

[0006] Raloxifene, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R^1 and R^3 are hydrogen and R^2 is 1-piperidinyl, is a nuclear regulatory molecule. Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and pharmacology was that of an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dep ndent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other cell types, raloxifene activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, raloxifene has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although raloxifene and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not easily predicted and is unique to each.

[0007] Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms.

[0008] The compounds used in the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635. In general, the process starts with a benzo [b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Substituted phenyl includes phenyl substituted once or twice with C_1-C_6 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

[0009] The compounds used in this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric and hypophosphoric. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate and tartarate. A preferred salt is the hydrochloride salt.

[0010] The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

[0011] Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

[0012] The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

[0013] Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions or powders. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc,

calcium and magnesium stearate, and solid polyethyl glycols.

[0014] The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

[0015] The particular dosage of a compound of formula I required to inhibit alopecia or hirsutism, according to this invention will depend upon the severity of the condition, the route of administration, and related factors chat will be decided by the attending physician. Generally, accepted and effective daily doses will be from 0.1 to 1000 mg/day, and more typically from 50 to 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed to effectively treat the problem.

[0016] It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring.

Formulations

[0017] In the formulations which follow, "Active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

[0018] Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

[0019] Examples of specific capsule formulations of raloxifene that have been made include those shown below:

Formulation 2: Raloxifene capsule

[0020]

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

[0021]

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

[0022]

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 5: Raloxifene capsule

[0023]

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

[0024] The specific formulations above may be changed in compliance with the reasonable variations provided.

[0025] A tablet formulation is prepared using the ingredients below:

Formulation 6: Tablets

[0026]

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

[0027] Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

Formulation 7: Tablets

[0028]

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

[0029] The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve.

The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

[0030] Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

Formulation 8: Suspensions

[0031]

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

[0032] The following compositions are prepared for topical application:

Formulation 9

[0033]

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.5 g
Active Ingredient	1.5-30 g
Isopropanol qs	100 g

Formulation 10

[0034]

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.5 g
Ethyl lactate	15.0 g
Active Ingredient	1.5-30 g
Isopropanol qs	100 g

Formulation 11

[0035]

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.0 g
Butylated hydroxytoluene	0.02 g
Active Ingredient	1.5-25 g
Ethanol qs	100 g

Formulation 12

[0036]

Ingredient	Quantity (mg/5 ml)
Hydroxypropylcellulose	1.5 g
Butylated hydroxytoluene	0.01 g
C_8-C_{12} fatty acid triglycerides	10.0 g
Active Ingredient	1.5-30 g
Isopropanol qs	100 g

[0037] Formulations 9-12 take the form of gels, and are intended for the topical treatment of acne.

Formulation 13

[0038]

Ingredient	Quantity (mg/5 ml)
Isopropanol	46.0 g
Active Ingredient	1.0-15 g
C_8-C_{12} fatty acid triglycerides	49.0 g

Formulation 14

[0039]

Ingredient	Quantity (mg/5 ml)
Ethanol	69.0 g
Ethyl lactate	10.0 g
Active Ingredient	1.5-20 g
C_8-C_{12} fatty acid triglycerides	30.0 g

Formulation 15

[0040]

Ingredient	Quantity (mg/5 ml)
Isopropanol	47.0 g
Acetone	10.0 g
Ethyl lactate	10.0 g
Active Ingredient	1-15 g
C_8-C_{12} fatty acid triglycerides	30.0 g

Formulation 16

[0041]

Ingredient	Quantity (mg/5 ml)
Ethanol	95.08 g
Butylated hydroxytoluene	0.02 g
Active Ingredient	1.5-25 g

[0042] Formulations 13, 14, 15, and 16 take the form of lotions.

Formulation 17

[0043]

Ingredient	Quantity (mg/5 ml)
White vaseline	50.0 g
Liquid paraffin	15.0 g
Refined paraffin wax	32.0 g
Active Ingredient	1-20 g

Formulation 18

[0044]

Ingredient	Quantity (mg/5 ml)
White vaseline	50.0 g
Liquid paraffin	13.0 g
Refined paraffin wax	32.0 g
Active Ingredient	1-20 g

[0045] Formulations 17 and 18 take the form of sticks.

TEST PROCEDURES

HIRSUTISM

[0046] Three to twenty women suffering from hirsutism are selected. These patients are initially scored for the extent and severity of hirsutism. The clinical evaluation is made by the methods described in the reference "Methods of Skin Research," John Wiley and Sons, pp 308-318 (1985), and the references cited therein. The patients receive 10-400 mg of an active compound of this invention per day as a single or split dose by oral administration. Alternatively, they apply a 10%, by weight of active ingredient, creme or lotion once or twice a day to the affected areas. The patient continues this protocol for six months. At appropriate intervals, re-evaluation by one of the methods described above would be made.

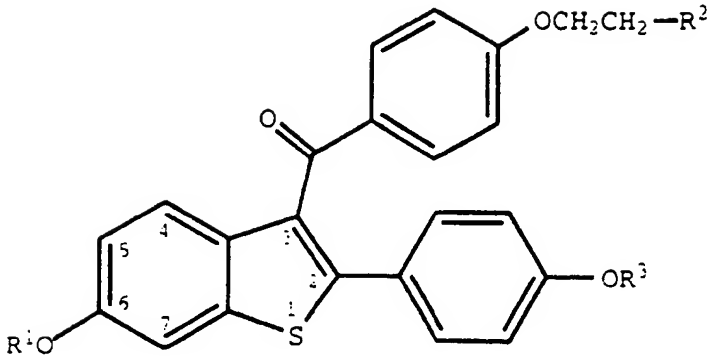
ALOPECIA

[0047] Three to twenty women suffering from female pattern alopecia are selected. These patients are initially scored for the extent and severity of the alopecia. This clinical evaluation is made by the methods described in "Methods of Skin Research," John Wiley and Sons, pp 308-318 (1985) and Habif, T., "Clinical Dermatology," C. V. Mosby Co., Chapter 23, pp 493-504 (1985); and references therein, herein incorporated by reference. Especially helpful in these evaluations is the"hair pluck" procedure and measurement of anagen to telogen ratio. The patients receive 10-400 mg of an active compound of this invention per day as a single or split dose by oral administration. Alternatively, the patients apply a 5-10% (by weight of a compound of this invention) as a creme, lotion, or shampoo to the affected area, once to twice a day. This protocol continues for six months. At appropriate intervals, re-evaluation by one of the methods described in the above references is made. A positive result is exhibited by an increase in the anagen to telogen ratio or an increase in the number of terminal hairs in the affected scalp region.

[0048] Utility of the compounds of the invention is illustrated by the positive impact they have on one or more of the symptoms when used in a study as above.

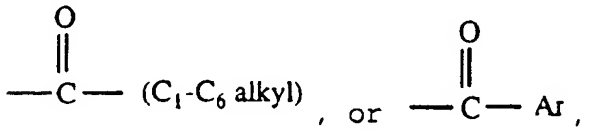
Claims

1. The use of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$,

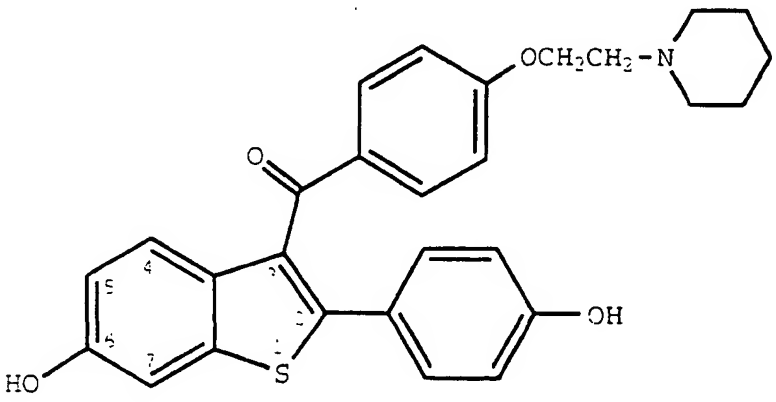


wherein Ar is optionally substituted phenyl;
R^2 is selected from the pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for inhibiting hirsutism in a woman.

2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.

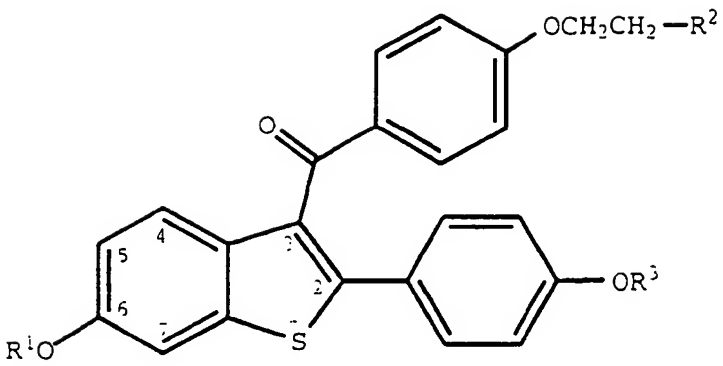
3. The use of Claim 1 wherein said medicament is prophylactic.

4. The use of Claim 1 wherein said compound is



or its hydrochloride salt.

5. The use of a compound having the formula



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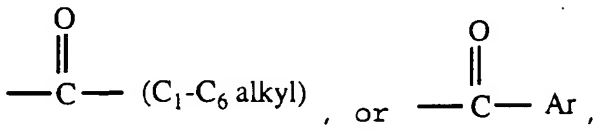
wherein R^1 and R^3 are independently hydrogen, $-CH_3$,

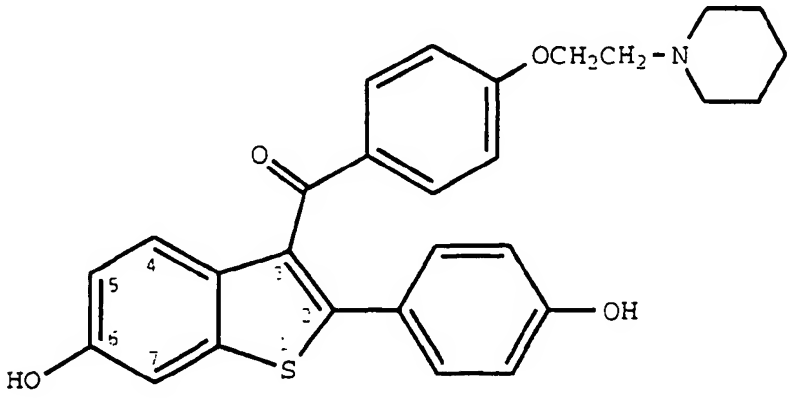


wherein Ar is optionally substituted phenyl;
R^2 is selected from pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for inhibiting alopecia in a woman.

6. The use of Claim 5 wherein said compound is the hydrochloride salt thereof.

7. The use of Claim 5 wherein said medicament is prophylactic.

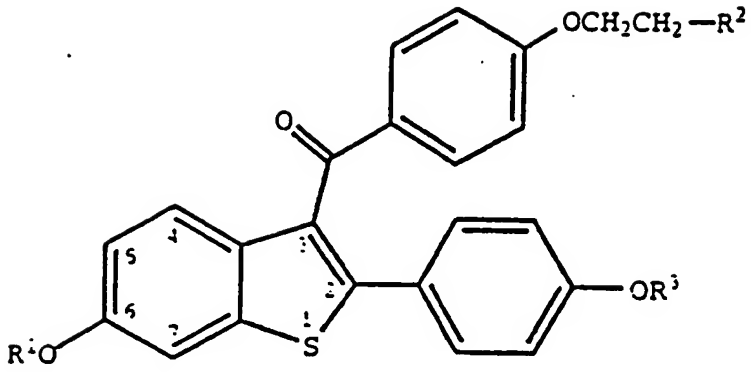
8. The use of Claim 5 wherein said compound is



or its hydrochloride salt.

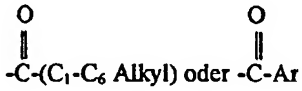
Pat ntansprüch

1. Verwendung einer Verbindung der Formel



(I)

worin R^1 und R^3 unabhängig für Wasserstoff, $-CH_3$,



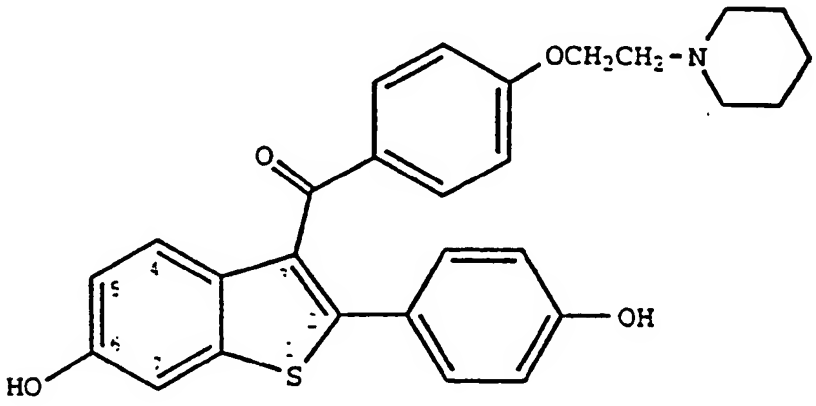
stehen, worin Ar für wahlweise substituiertes Phenyl steht,
R^2 ausgewählt ist aus Pyrrolidino und Piperidino,

oder eines pharmazeutisch annehmbaren Salzes oder Solvats hiervon zur Herstellung eines Arzneimittels zur Hemmung von Hirsutismus bei einer Frau.

2. Verwendung nach Anspruch 1, worin die Verbindung das Hydrochloridsalz hiervon ist.

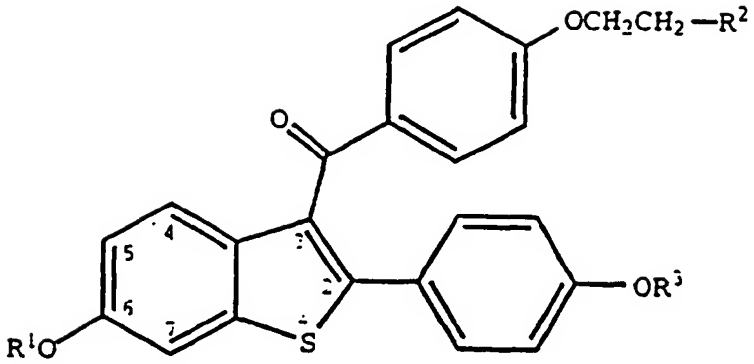
3. Verwendung nach Anspruch 1, worin das Arzneimittel prophylaktisch ist.

4. Verwendung nach Anspruch 1, worin die Verbindung folgende ist

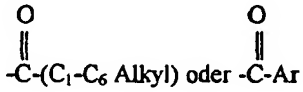


oder das Hydrochloridsalz hiervon.

5. Verwendung einer Verbindung der Formel



worin R^1 und R^3 unabhängig für Wasserstoff, $-CH_3$,



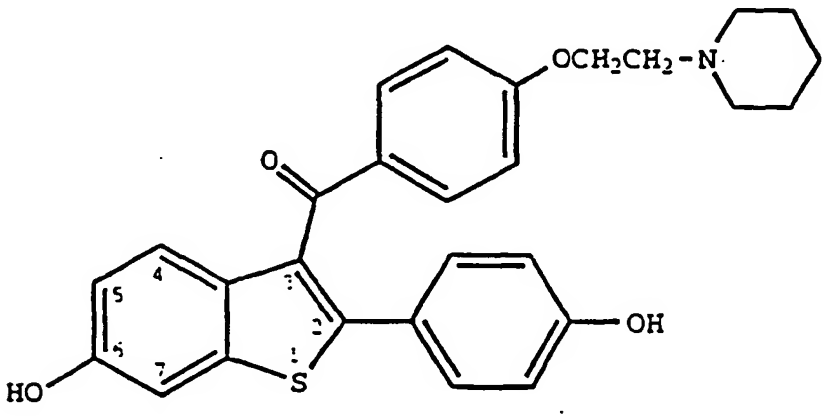
stehen, worin Ar für wahlweise substituiertes Phenyl steht,
R^2 ausgewählt ist aus Pyrrolidino und Piperidino,

oder eines pharmazeutisch annehmbaren Salzes oder Solvats hiervon zur Herstellung eines Arzneimittels zur Hemmung von Alopecia bei einer Frau.

6. Verwendung nach Anspruch 5, worin die Verbindung das Hydrochloridsalz hiervon ist.

7. Verwendung nach Anspruch 5, worin das Arzneimittel prophylaktisch ist.

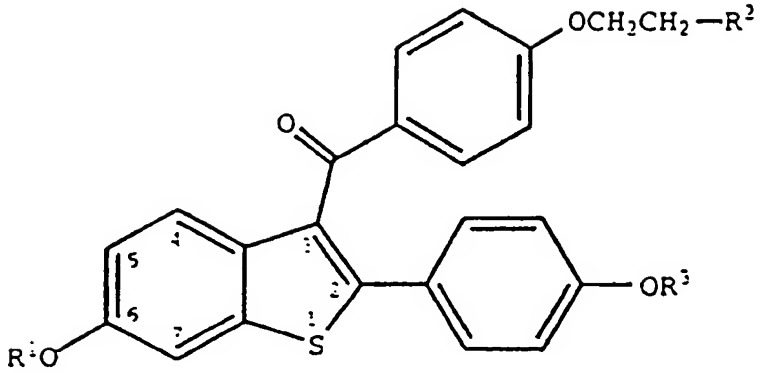
8. Verwendung nach Anspruch 5, worin die Verbindung folgende ist



oder das Hydrochloridsalz hiervon.

Rev ndicati ns

1. Utilisation d'un composé répondant à la formule



(I)

dans laquelle

R^1 et R^3 représentent indépendamment un atome d'hydrogène, un groupe $-CH_3$, un groupe

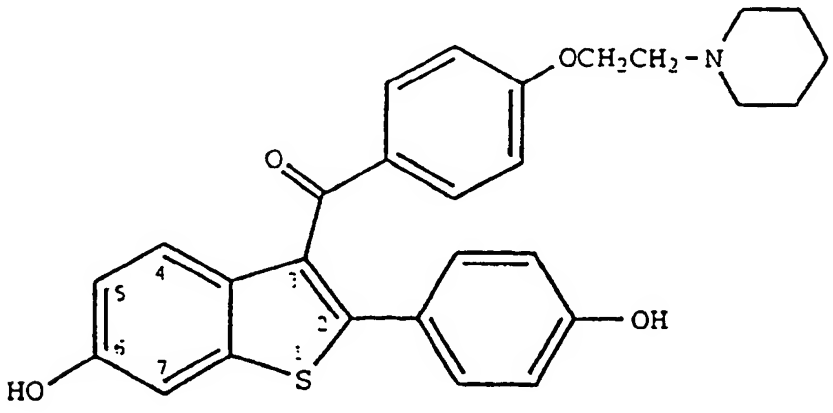
$$-\overset{O}{\overset{\|}{C}}\text{-(alkyle en } C_1\text{-}C_6\text{) ou un groupe } -\overset{O}{\overset{\|}{C}}\text{-Ar,}$$

où Ar représente un groupe phényle facultativement substitué ;
R^2 est choisi parmi un groupe pyrrolidino et un groupe pipéridino ; ou d'un sel ou solvate pharmaceutiquement acceptable de celui-ci, dans la préparation d'un médicament pour inhiber l'hirsutisme chez une femme.

2. Utilisation selon la revendication 1, dans laquelle ledit composé est le sel d'hydrochlorure de celui-ci.

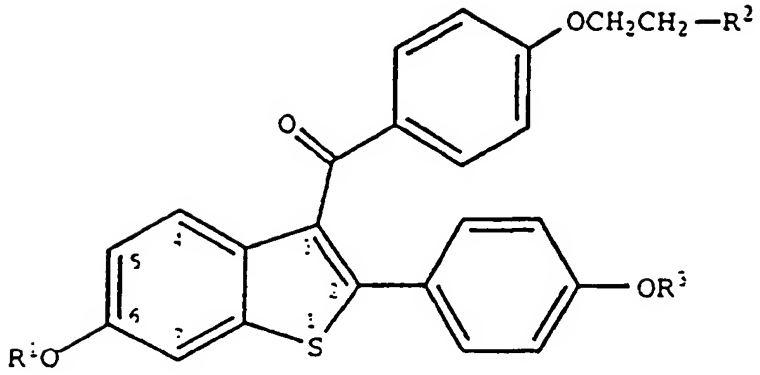
3. Utilisation selon la revendication 1, dans laquelle ledit médicament est prophylactique.

4. Utilisation selon la revendication 1, dans laquelle ledit composé est



ou son sel d'hydrochlorure.

5. Utilisation d'un composé répondant à la formule



(I)

dans laquelle

R^1 et R^3 représentent indépendamment un atome d'hydrogène, un groupe $-CH_3$, un groupe

$$-\overset{O}{\overset{\|}{C}}-(\text{alkyle en } C_1\text{-}C_6) \text{ ou un groupe } -\overset{O}{\overset{\|}{C}}-Ar,$$

où Ar représente un groupe phényle facultativement substitué ;
R^2 est choisi parmi un groupe pyrrolidino et un groupe pipéridino ; ou d'un sel ou solvate pharmaceutiquement acceptable de celui-ci, dans la préparation d'un médicament pour inhiber l'alopécie chez une femme.

6. Utilisation selon la revendication 5, dans laquelle ledit composé est le sel d'hydrochlorure de celui-ci.